Vitamin E and haemolytic anaemia in premature infants

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Lo, S. S., Frank, D., and Hitzig, W. H. (1973). *Archives of Disease in Childhood*, 48, 360. **Vitamin E and haemolytic anaemia in premature infants.** Studies in 50 premature babies aged 6 to 8 weeks showed that vitamin E plays a significant role in the pathogenesis of the 'anaemia of prematurity'. Administration of 10 mg/day vitamin E orally elicited a clear-cut clinical and haematological response.

There was a relation between the type of nutrition and the onset of anaemia, anaemia regularly developing within 2 weeks of changing from human milk to a powdered cow's milk formula. Susceptibility to haemolysis was quantitated by measuring the free haemoglobin after exposure of the erythrocytes to hydrogen peroxide. This peroxide haemolysis was increased when the vitamin E level in the blood was below 0.6 mg/100 ml. It became normal a few days after vitamin E administration and the consequent rise in blood concentration.

It is concluded that a supplement of vitamin E is advisable from the 10th day onwards in premature infants who are artificially fed.

Several distinct features, ranging from encephalomalacia to hepatic or renal degeneration and nutritional muscular dystrophy, have been described in vitamin E deficient animals (Dacie, 1960; Darby *et al.*, 1949; Darby, 1968). Vitamin E depletion is often found in humans with malabsorption syndromes, but several authors failed to find clear-cut clinical manifestations (Binder *et al.*, 1965; Blanc, Reid, and Andersen, 1958; Gerloczy *et al.*, 1961; Gordon, Nitowsky, and Cornblath, 1955; Gresham, Cruickshank, and Valentine, 1958; Kerner and Goldbloom, 1960; Harries and Muller, 1969; Majaj *et al.*, 1963; Oppenheimer, 1956; Pappenheimer and Victor, 1946; Weinberg *et al.*, 1958). Systematic studies of Majaj (1960) and Majaj *et al.* (1963) revealed, however, the causal relation between tocopherol deficiency and anaemia. The human infant is born with small body stores of tocopherols, and conventional artificial feeding results in a slower enhancement of these stores than does breast feeding (Darby, 1968). Vitamin E deficiency has recently been considered to be one of the causes of haemolytic anaemia in the premature infant (Hassan *et al.*, 1966; Oski and Barness, 1967; Ritchie *et al.*, 1968). We have studied 50 premature

babies who developed varying degrees of anaemia at the age of 6 to 8 weeks and studied the effect of administering vitamin E.

Materials and methods

50 unselected premature babies with birthweight less than 2000 g were studied at weekly intervals from the age of 2 weeks onwards. In 30 healthy infants born at term the same tests were made once between the ages of 27 and 53 days. The study group was divided equally. 25 prematures received α -tocopherol (Ephynal, Roche) 10 mg daily by mouth when the first signs of haemolysis appeared, i.e. at the age of 40 ± 13 days. Of the other 25 prematures, 12 were not treated at all, and 13 were treated 2 to 4 weeks after having developed signs of haemolytic anaemia (low haemoglobin, high reticulocyte count). There was no evidence of rhesus or other blood group incompatibility, haemoglobinopathy, enzymopathy, or other known causes of increased haemolysis in any of the infants admitted to the study. Routinely, these infants received oral vitamin C, iron, and vitamin D daily from the second week onwards. Nutrition: 6 were fed with human milk, 4 with commercial cow's milk formula only, and 34 received human milk until they reached 2000 g body weight and were then changed to commercial milk formulae (either Prodiecton or Guigoz). The vitamin E content of these milk formulae was 30 to 40 $\mu\text{g}/100$ ml reconstituted milk. In contrast, human milk contains 100 to 480 (mean 240) μg

tocopherol/100 ml (Harris, Quaife, and O'Grady, 1952).

Hb, haematocrit, reticulocytes, and peripheral blood films were determined or inspected weekly by conventional standard methods. The reticulocyte count per 1000 red cells was related to the actual Hb value by the formula

$$\text{Retics (\%)} \times \text{Hb (g/100 ml)} / 16 = \text{Retics (corrected)\%} \quad (\text{Dacie, 1960}).$$

Hydrogen peroxide haemolysis test was performed according to the method originally described by Rose and György (1952) and modified by Gordon *et al.* (1955). Serum tocopherol was assayed by the method of Hashim and Schuttringer (1966)*. Hydrogen peroxide haemolysis test was carried out at approximately weekly intervals on all the patients, and on 30 normal healthy children of varying ages as a control group.

Results

The control study on 30 normal children (Frank, 1970) showed that H_2O_2 haemolysis never exceeded 10%, which is consistent with the values given by Rose and György (1952) and Gordon *et al.* (1955). The serum levels of vitamin E among this group of children were found to be above 0.6 mg/100 ml, whereas others reported the critical level to be 0.5 mg/100 ml (Darby *et al.*, 1949; Gordon *et al.*, 1955; Mackenzie, 1954). However, there was a clear correlation between serum vitamin E levels and *in vitro* peroxide haemolysis tests (Fig. 1),

FIG. 1.—Relation between serum tocopherol levels and H_2O_2 -haemolysis in 15 premature and 30 term babies artificially fed, aged 27 to 53 days (Frank, 1970).

with invariably some increased susceptibility of the red cells to the haemolytic action of hydrogen peroxide when the vitamin E level was below 0.6 mg/100 ml.

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FIG. 2.—Effect of vitamin E administration on *in vitro* H_2O_2 -haemolysis in 50 premature infants.

Among our 50 premature babies studied, 38 developed signs of haemolytic anaemia at the age of 40 ± 13 days, with Hb levels of 9.7 ± 1.3 g/100 ml (mean $\pm$ SD), reticulocytosis of $3.83 \pm 1.72\%$ (corr.), *in vitro* peroxide haemolysis tests of $58.3 \pm 22.8\%$, and vitamin E levels ranging from 0.12 to 0.48 mg/100 ml in the serum; 6 were fed with human milk only and showed no evidence of anaemia; and the remaining 6 were discharged home at the age of 4 weeks with normal peroxide haemolysis test.

Among the 38 infants with evidence of haemolytic anaemia, 25 patients received α -tocopherol-acetate 10 mg daily by mouth; this was followed by an increase in Hb from a mean of 9.6 ± 1.1 to 10.7 ± 1.0 g/100 ml, decrease in the reticulocyte counts from a mean of $3.96 \pm 1.69\%$ (corr.) to $1.95 \pm 1.03\%$ (corr.), a fall of the *in vitro* peroxide haemolysis tests (mean $3.5 \pm 2.4\%$) and a rise in serum vitamin E levels to above 0.5 mg/100 ml after 13 to 21 days' treatment (Fig. 2 and Table I). These changes were all statistically significant (Table II).

TABLE I

Haematological findings in 25 premature infants before and after administration of vitamin E

	Before vitamin E therapy	After vitamin E therapy	P
H_2O_2 haemolysis (%)	58.3 ± 22.8	3.5 ± 2.4	<0.0005
Reticulocytes (corrected) (%)	39.6 ± 16.9	19.5 ± 10.3	<0.0005
Hb (g/100 ml)	9.6 ± 1.1	10.7 ± 1.0	<0.0005

*Reticulocyte count corrected for anaemia by multiplying it by the factor Hb (g/100 ml)/16 (Dacie, 1960).

TABLE II
Correlation between type of feeding and haemolysis in
50 premature infants

Feeding	No. of patients with haemolysis	No. of patients without haemolysis
Human milk	0	6
Human milk (discharged at 4 wk old)	0	6
Commercial milk formulae	4	0
Human milk, then commercial milk formulae	34	0
Total	38	12

The remaining 13 patients were sent home on vitamin E but only 2 were seen again in the out-patient department; both responded well to treatment.

Examination of the blood smears before treatment showed no specific anomalies other than a variable degree of anisocytosis, poikilocytosis, and polychromasia and, in a few cases, small numbers of spherocytes. After treatment, in the majority these features in the blood picture became less marked.

Clinically, no abnormality was observed in the vitamin E deficient babies. In 2 cases oedema of the lower extremities was present at 5 and 6 weeks of age, respectively; both had serum protein levels of 4.3 g/100 ml (normal value for their age 5.65 ± 0.40). Serum electrolytes were normal. Other causes of oedema were excluded. In one case, there was an unexplained swelling and redness of the finger joints: this, together with the haemolytic anaemia, subsided after 3 weeks' administration of vitamin E orally (Fig. 3). Fig. 3 and 4 illustrate

FIG. 3.—Clinical and haematological response of a premature infant given a 6-week course of vitamin E 50 mg daily orally.

FIG. 4.—Haematological response of a premature infant with haemolytic anaemia given a 4-week course of vitamin E 10 mg daily.

two cases of vitamin E deficiency and their response to treatment.

Comparative studies were done on two pairs of twins and one pair of babies with similar birth-weight and gestational age: one of each of these three pairs of infants was given vitamin E on the day of diagnosis of haemolytic anaemia and the other of the pair was kept under observation for 4 weeks before the administration of vitamin E. Fig. 5 illustrates the results in one of these pairs. In the early treated cases anaemia and reticulocytosis, and positive peroxide haemolysis test were present. After treatment with vitamin E these signs disappeared. No significant differences with respect to weight gain were observed between the early and late treated patients.

A relation appeared to exist between the type of feeding and the onset of anaemia: 34 out of the 38 patients were initially fed with human milk and were subsequently changed to commercial milk formulas (Prodieton or Guigoz) when their weight approached 2000 g. Anaemia tended to develop, along with a positive peroxide haemolysis test, 10 to 14 days after the infants' feed had been changed to the milk formulae. The vitamin E content of these formulae was 30 to 40 $\mu\text{g}/100\text{ ml}$ reconstituted milk, compared with an average value of 240 $\mu\text{g}/100\text{ ml}$ in human milk (Harris *et al.*, 1952).

Comment

When discussing the anaemia of prematurity, the normal haematological values and the course

FIG. 5.—(a) Twin A treated early with vitamin E 10 mg daily. Increase in Hb, decrease in reticulocytes, and normal H_2O_2 -haemolysis test after 2 weeks' treatment. (b) Twin B, after being observed for 4 weeks, was given vitamin E 10 mg daily. Anaemia, reticulocytosis, and positive H_2O_2 -haemolysis test persisted until treatment was begun.

of the Hb concentration and reticulocytes must be laid down. For term babies at age 7 weeks the average Hb level is 12.7 ± 1.64 g/100 ml (Guest and Brown, 1957); lower values have been reported in prematures (Gairdner, Marks, and Roscoe, 1955; Seip and Halvorsen, 1956). Schulmann (1959) has divided the anaemia of prematurity into 3 phases during the first year of postnatal life: an early, intermediate, and late phase of anaemia. In the early phase Hb falls to a minimum of 8 to 9.5 g/100 ml at approximately 7 weeks of age. Two mechanisms are thought to be involved: (a) a marked decrease in erythropoietic activity beginning shortly after birth, and (b) a decrease in the life span of the erythrocytes (Vest, 1967).

However, the factor or factors that may contribute to these mechanisms and the relative influence of each remain unknown. Vitamin E deficiency as a cause of haemolytic anaemia in the premature infant was first reported by Oski and Barness (1967) and further supported by Ritchie *et al.*, 1968. On the other hand, other workers have found no difference between the Hb levels of premature infants that are tocopherol deficient and tocopherol sufficient (Goldbloom and Cameron, 1963; Panos *et al.*, 1968).

The patients in our study had Hb levels below and reticulocyte counts above the normal values of term babies (Guest and Brown, 1957), indicating that there was increased haemolysis. (It should be noted that the reticulocyte count when corrected for the degree of anaemia is numerically smaller than without this correction. For example, the uncorrected value for the reticulocyte level of the patient in Fig. 4 who had 8.0 g/100 ml Hb is twice as high (136%) as the corrected value (68%).) Our observations showed a close correlation between vitamin E concentration of the plasma and susceptibility to haemolysis in H_2O_2 (Fig. 1).

In breast-fed infants we have noticed that severe anaemia did not occur, whereas in artificially-fed babies anaemia was invariably present. Nitowsky *et al.* (1962) found that term infants fed on partially skimmed cow's milk showed a decrease in plasma tocopherol; in the first 10 days the plasma level was 0.26 mg/100 ml, and by 30 days of age the level had fallen to an average of 0.13 mg/100 ml. Oral supplementation with small doses of tocopherol led to a prompt rise in plasma levels. Compared with the breast-fed infant weighing 2000 g who receives about 0.3 to 3 mg tocopherol daily, an artificially-fed baby of the same weight receives only about 0.03 to 0.12 mg. The requirements of the normal premature infant are met by a formula containing 3.0 mg of α -tocopherol per litre (Goldbloom and Cameron, 1963). These figures explain why only infants who are artificially fed are prone to vitamin E deficiency.

The mechanism of the haemolysis in vitamin E deficiency involves the following facts (Darby, 1968). Tocopherol is a potent antioxidant: it stabilizes polyunsaturated lipids and minimizes lipid peroxidation damage. In the presence of vitamin E deficiency, lipid peroxides accumulate rapidly (Century and Horwitt, 1960) and they bind free sulphhydryl groups (Lewis and Wills, 1962). Red cells are known to become hyper-permeable to cations when membrane sulphhydryl groups are blocked or oxidized (Jacob and Jandl, 1962 a, b). With a breakdown in cation gradients,

osmotic swelling ensues and haemolysis occurs.

Among the cases studied we failed to observe generalized oedema in vitamin E deficient premature babies as described by Hassan *et al.* (1966) and Ritchie *et al.* (1968). In the only two cases with oedema of the lower extremities, the oedema was attributed to hypoproteinaemia, but vitamin E deficiency might have been a contributory factor. Gerloczy *et al.* (1961) have reported 752 cases of 'sclerema neonatorum' among 16,033 premature babies; all had low levels of serum tocopherol and responded to oral administration of tocopherol acetate. The child in our series with unexplained swelling of the fingers might be regarded as having suffered a localized form of sclerema, which appeared to regress promptly after vitamin E administration. Tocopherol deficiency as a cause of oedema was also described in animal experiments (monkeys: Dinning and Day, 1957; Dinning, 1962; Fitch, 1968; Porter, Fitch, and Dinning, 1962; chickens: Bird and Culton, 1940; rats: Tsen and Collier, 1960).

Since the discovery of vitamin E half a century ago, various deficiency syndromes have been recognized in experimental animals and in man. Little is known, however, about signs of clinical toxicity of tocopherol excess in man. It has been reported that a normal adult can tolerate a total of 296 g vitamin E over a period of 93 days with a resulting high level in his plasma (2.26 mg/100 ml), but no abnormal clinical signs could be shown (Hillman, 1957). All these toxicity studies have been carried out on adult animals and adult human beings. Because other drugs have earlier apparently been shown to be 'safe', but have later turned out not to be innocuous for premature infants (oxygen, vitamin K analogues, sulphasoxazole, chloramphenicol), administration of vitamin E to premature infants should be carried out cautiously. We have given 10 mg daily of vitamin E in the form of α -tocopherol acetate.

Body stores of tocopherol of the premature infant are lower at birth than those of the term infant (Dju, Mason, and Filer, 1958; Woodruff *et al.*, 1964; Darby, 1968). After birth the relatively rapid weight gain of these babies, together with their limited ability to absorb fat from the usual cow's milk formulae, result in a very poor net gain of vitamin E. It has been shown by Oski and Barness (1967) and confirmed by our own observation that administration of vitamin E to premature infants, particularly to those fed artificially, reduces both the severity of anaemia and the marked reticulocytosis commonly observed. It appears reasonable to supplement the diet for

premature infants with vitamin E from the 10th day onwards, i.e. when their serum tocopherol levels are beginning to fall (Mackenzie, 1954; Nitowsky, Cornblath, and Gordon, 1956; Wright, Filer, and Mason, 1951). We recommend a daily dose of 10 mg vitamin E (tocopheryl-acetate) to infants of low birthweight, though others have found that as little as 0.5 mg/kg α -tocopherol daily suffices (Nitowsky *et al.*, 1962).

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